# COMPUTATIONAL EXPLORATION ON POTENTIAL TARGETS OF *MYCOBACTERIUM TUBERCULOSIS* AND IDENTIFICATION OF NOVEL LEADS

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*Submitted by*

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**Abstract:**

There is an extreme need for new and better drugs to treat tuberculosis due to long and complex treatment regimens and a rising problem of drug resistance. Drug designing efforts have increased over the past few years, with a larger focus on modern high-throughput screening technologies. New targets and drug candidates are being investigated by researchers across the world to fulfill the extreme need of novel drugs for tuberculosis and old targets are also being investigated with advent of computational method. Recent study shows, Cyclopropane mycolic acid synthase 1(CmaA1) and Glucose-1-phosphate thymidylyltransferase (RmlA) in *Mycobacterium tuberculosis* are attracted as drug target. Mycobacterial CmaA1 is one of the potential drug target, which is responsible for the maturation of mycolic acids by cyclopropanation, thus involve in the persistence and virulence of *M. tuberculosis*. RmlA, enzyme is involved in the biosynthesis of L-rhamnose, of *M. tuberculosis* cell wall.

In present study, we are planning to analysis these targets by using a comparative modeling approach. So employing in *silico* approaches to resolve and characterize the structure of these enzymes by molecular modeling and simulation techniques. This information could be exploiting for designing of more effective leads for *M. tuberculosis* enzymes.

**1. Introduction:**

Tuberculosis (TB) caused by *Mycobacterium tuberculosis* (Mtb) remains a major global health problem. According to 'global tuberculosis report 2017' by the world health organization (WHO) it causes ill-health for approximately10 million people each year and is one of the top ten causes of death worldwide. For the past 5 years, it has been the leading cause of death from a single infectious agent, ranking above HIV/AIDS (Global Tuberculosis Report, 2017). Given the alarming rise of resistance to antitubercular drugs worldwide, finding new cellular targets and developing new analogues or new compounds with greater potency against already known targets are both important aspect in fighting drug-sensitive and drug-resistant *M. tuberculosis* strains (Roberto et al., 2016). Mycobacterial mycolic acid cyclopropane synthases (PcaA, CmaA1, and CmaA2) are responsible for site-specific modifications of mycolic acids. These structures provide a foundation for rational-drug design, which may lead to the development of new inhibitors (Huang et al., 2001).RmlA gene, is essential for mycobacterial growth and lack of RmlA activity has profound negative effects on bacterial cell morphology. RmlA is thus a potential target for the development of new antituberculosis drugs (Qu et al., 2007).

Present study is aimed to explore structures of these antituberculosis targets by comparative modeling study and simulation approach. This exploration will help to design potential leads of these selected targets.

**2. Review of Literature and Development in the subject:**

Identification of new drug targets is vital for the advancement of drug discovery against *Mycobacterium tuberculosis*, especially given the increase of resistance worldwide to first- and second-line drugs. Because traditional target-based screening has largely proven unsuccessful for antibiotic discovery (Ioerger et al., 2013).

The oldest such as the enoylreductase InhA which is constantly repurposed with new inhibitors, through the well assessed targets like thegyrase, the ATP synthetase or the RNA polymerase, up to the hot promiscuous targets decaprenylphosphoryl-Dribose oxidase DprE1 and the mycolic acid transporter MmpL3, or the newly validated and promising targets likethe CTP synthetase(Roberto et al., 2016).

Phenotypic screening seems to be a more promising approach to identify compounds active against MDR-TB than the target-based approach. Despite this, the search for new compounds active against resistant-TB remains a challenge. The molecular mechanism involved in the resistance and its possible targets is still not completely understood (Felipe et al., 2017).

The emerging targets include GlgE, enzymes involving mycolic acid cyclopropanation, DprE1/DprE2, MshC, HisG, AtpE, Def and methionine amino peptidase, etc., which are crucial for the actively growing mycobacteria. Few new chemical entities such as dioctylamine, benzothiazinone, dinitrobenzamides, dequalinium chloride, nitrobenzothiazole, diarylquinoline, TMC207, LBK-611 and 2, 3-dichloro-1, 4-naphthoquinones are in clinical trials. However, the new drug discovery strategies should include multidisciplinary approaches to identify and understand the structure and dynamic behavior of the potential drug targets (Lamichhane, 2011; Choudhury et al., 2015).Enzymes involved in L-rhamnose synthesis of Mtb, which plays an essential structural role in the cell wall formation. Mycobacterial cell wall is essential for viability; it represents a very attractive for new antibacterial agents target (Chaitanya et al., 2010; Crick and Brennan, 2000).

**3. Objective of Research:**

Objective of research is to find novel leads which will work again *Mycobacterium tuberculosis*.

**4. Methodology to be adopted:**

The overall objective of the study to carry out molecular modeling activities on the selected targets belonging to tuberculosis. It will perform by using computational approach involving molecular modeling and docking. Several online resources as well as licensed software will be used for the implementation of the computational approach.

**5. Importance of study/society application:**

- International status:

Tuberculosis (TB) has existed for millennia and remains a major global health problem. It causes ill-health for approximately 10 million people each year and is one of the top ten causes of death worldwide. For the past 5 years, it has been the leading cause of death from a single infectious agent, ranking above HIV/AIDS. In 2016, 6.3 million new cases of TB were reported (up from 6.1 million in 2015), equivalent to 61% of the estimated incidence of 10.4 million (Global tuberculosis report, 2017).

- National status:

India one of the countries with the highest burden of TB in the world, accounts for approximately one fifth of the global incidence. In 2013, 2.1 out of the 9.0 million estimated global annual incidences of TB cases occurred in India (Padmapriyadarsini et al., 2016).

- Significance of the study:

Tuberculosis (TB) is a major infectious disease that knows no geographic boundary and accounts for 9 million new cases and approximately 1.5 million deaths each year (Global tuberculosis report, 2017). Introduction of the phenotypic screens as an efficient tool for the identification of active compounds for tuberculosis drug discovery has improved the possibility to find new effective targets (Roberto et al., 2016).

Thus it is necessary to understand different potential targets to develop novel inhibitor.

**6. Proposed work Plan:**

Year I: Course work, analysis of selected *M. tuberculosis* targets.

Year II: Molecular modeling and docking studies for identification of leads.

Year III: Data analysis, writing papers and thesis

**7. References:**


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